REMARKS

Applicant thanks the Office for the attention accorded the present Application in the January 29, 2003, Office Action. In that Action, Claims 1-10 and 17 were rejected under 35 USC §103(a) as being unpatentable over Pearle, Carruthers et al., Abby et al., Oakley et al., and Behounek et al. in view of Rork et al., and Claim 18 was allowed.

Applicants have amended Claim 18 to allow for the addition of excipients or other pharmaceutical carriers.

The Office admits that the references Pearle, Carruthers et al., Abby et al., Oakley et al., and Behounek et al. do not expressly teach the incorporation of beta-blockers such as timolol, metoprolol, atenolol, and propranolol, and HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B6, and vitamin B12 into a single dosage unit.

The Office cites Rork et al. for the proposition that Rork et al. teaches a sustained release system that can include beta-blockers such as timolol, metoprolol, atenolol, and propranolol and statin cholesterol lowering agents such as simvastatin, pravastatin, and lovastatin. The Office then concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate beta-blockers such as timolol, metoprolol, atenolol, and propranolol with HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B6, and vitamin B12 into a single once-a-day dosage unit. The Office supports its conclusion by stating that there is no teaching or disclosure in Rork et al. expressly teaching against using more than

one active in such once-daily formulation.

Applicants respectfully traverse.

As previously explained, the present invention is based upon recognizing the serious consequences stemming from a failure of patients to avail themselves of, to receive and to take medication (in other words, patient compliance), particularly beta-blockers and cholesterol lowering agents. The present application teaches that the problems of achieving compliance include the inconvenience of taking multiple dosage units over a long period of time and confusion with multiple medications particularly in older individuals, the age group in which these cardio-preventative medications are typically required. (Applicants' Disclosure: Page 4, lines 18-21). Large studies indicate that tens of thousands of lives could be saved each year if more people were utilizing a beta-blocker after having a heart attack. (Applicants' Disclosure: Page 4, lines 7-15). The failure of patients to avail themselves of such treatment underscores the present need for the formulations of the present invention.

The Office relies on its conclusion that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate beta-blockers with HMG-CoA reductase inhibitors into a single dosage unit. To circumvent the lack of teaching or suggestion to support its conclusion, the Office relies on the convoluted argument that Rork et al. lack an express teaching against using more than one active in such once-daily formulation. The Office appears confused. A requirement of an express teaching against using more than one active is not the standard.

To establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. See In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Most if not all inventions arise from a combination of old elements. See In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). Thus, every element of a claimed invention may often be found in the prior art. See id. However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. See id.

Rork et al. may not expressly teach against using more than one active, however, there is no teaching or suggestion to use more than one active. In fact, Rork et al. discloses a controlled release nifedipine delivery device. Rork et al. discuss using their device for the delivery of a beneficial agent as a gelatinous dispersion consisting of (1) a core which contains a beneficial agent, a polymer which forms gelatinous microscopic particles upon hydration and, if desired, an agent to modulate the hydration of the polymer and (2) an impermeable, insoluble coating which adheres to and surrounds the core and contains apertures which provide an area for the hydration and release of a dispersion comprising gelatinous microscopic particles. Rork et al. disclosed the use of only a single beneficial agent, i.e. one drug at a time, in their device. The use of the transition "consisting of" excludes the inclusion of a second

beneficial agent within their delivery device. This is further evidenced by their definitions and the written description of the device.

Rork et al. defined "compressed core" as an admixture of a beneficial agent, a polymer and other ingredients that may affect any of the rate of production of dispersion, the stability of the components of the dosage form or the mixing or compression characteristics of the admixture. (Column 5, lines 4-10). The beneficial agent is **a** singular agent. Each time Rork et al. use the term "drug" it is in its singular form, which connotes one drug. In fact, Rork et al. defined the term "drug" and its equivalents in the specification and the accompanying claims to include any physiologically or pharmacologically active substance (singular) that produces a localized or systemic effect. (Column 5, lines 21-25).

Rork et al. continues at Column 5, line 30 to say "**the** active drug", at Column 5, line 48 to say "**the** dissolved drug", at Column 7, line 33 to say "**the** drug can be", at Column 7, line 34 to say "also, **the** drug can be mixed", at Column 8, line 24 to say "the core compartment containing **the** drug", at Column 8, line 47 to say "in cases where **the** drug", at Column 8, line 55 to say "generally the core will contain 1% to 50% by weight, of **a** beneficial agent". In each instance, Rork et al. describe the drug as **a single** drug, not a combination of two beneficial agents combined together in a single dosage unit. Every one of the 12 examples provided by Rork et al. contain only **one active, beneficial agent** such as indomethacin (Examples 1-4), simvastatin (Examples 5 and 7), lovastatin (Examples 6, 8, 10 and 11), acetaminophen (Example 9), or nifedipine

(Example 12). Every instance where a beneficial agent or drug is referred to, it is used singularly and **n t** in combination with a second, different beneficial agent.

Rork et al. then list a large number of different drugs beginning in Column 5, line 63 to Column 7, line 17. Rork et al. provide this simply as a list of various drugs that could be **individually** used in their device. Rork et al. disclosure is conspicuously absent of any examples of a formulation containing a beta-blocker and an antihyperlipidemic agent together in a single dosage unit.

When considered in the context of the teaching of the entire Rork reference as required by the Federal Circuit, there is not substantial evidence of record in Rork et al. to extrapolate this teaching to the combination of agents together in a single formulation dosage unit. At most, the combined teachings suggest that each agent may be delivered and released in situ and that one drug delivery device controls the in situ production and release of a dispersion containing a single, beneficial agent. There is not relevant evidence as a reasonable mind might accept as adequate to support the conclusion that, where there are a plurality of beneficial agents listed and each is capable of being delivered by a control release device, only one control release device provides the delivery for a plurality of beneficial agents together.

Applicants provide further objective evidence in support of Applicants' claim of nonobviousness by way of the Declaration of Dr. Jerry H. Gurwitz. Dr. Gurwitz is a Professor of Medicine at the University of Massachusetts Medical School, Executive Director of the Meyers Primary Care Institute and one of the foremost authorities in the

country for the treatment of the elderly and on the subjects of adverse drug events, drug prescribing and utilization patterns, and clinical decision-making in the elderly patient. Dr. Gurwitz may be considered one of extraordinary skill in the art, yet even Dr. Gurwitz believes that Applicants' invention is nonobvious and will provide a means to overcome problems in patient compliance and to improve upon present under-utilization of cardiovascular treatments.

Dr. Gurwitz has no financial interest in Applicants' invention and will not financially benefit directly or indirectly from the patentability of the present invention. In fact, such a dosage unit for cardioprotection would likely reduce the number of cases of recurring myocardial infarction that he treats each year.

Dr. Gurwitz's declaration is relied upon as evidence of the knowledge possessed by not only one of ordinary skill in the art but also by the knowledge possessed by one having a higher level of knowledge than one of ordinary skill in the art (specialist in treating the elderly where noncompliance especially with multiple medications is a problem). Dr. Gurwitz's Declaration is also relied upon to support the persuasiveness of Dr. Dean's declaration. As a disinterested party, Dr. Gurwitz's opinion evidence must be given serious weight.

Dr. Gurwitz's declaration further confirms that one of extra-ordinary skill in the art is not one who undertakes to innovate. He knows first hand the problems with patient noncompliance in multiple medication treatment regimens, especially in the elderly. He is also aware of the need in the field to overcome these problems.

Secondary considerations must be given due weight by the examiner and the Board of Appeals during ex parte prosecution. *In re Semaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Objective evidence, composed of real-world facts, is entitled to **great weight** in a case. *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 221 USPQ 1 (Fed. Cir. 1984) (emphasis added). Although objective factual evidence of obviousness or nonobviousness is preferable to opinion testimony, such testimony is entitled to some weight. Opinion testimony by a party with a direct interest in the litigation is less persuasive than that of a disinterested party, but it may still be relied upon. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). The secondary considerations are . . . essential components of the obviousness determination. *In re Rouffet*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). The consideration of the objective evidence presented by the patentee is a necessary part of the obviousness determination . . . The objective evidence of non-obviousness may be used to rebut a prima facie case of obviousness based on prior art references. *WMS Gaming, Inc. v. International Game Technology*, 184 F3.d 1339, 51 USPQ2d 1385 (Fed. Cir. 1999). Recognition of need and difficulties encountered by those skilled in the field are classical indicia of unobviousness. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

Applicants have provided objective evidence (1) to show the pharmaceutical and medical industries failure to recognize the need for a single dosage unit as a means to

enhance patient compliance to cardiovascular treatment regimens incorporating beta-blockers and lipid lowering agents while the industry recognized that compliance problems exist, (2) to show the knowledge level of one of ordinary skill in the art, and (3) to show the failure of existing modes of enhancing patient compliance and under-utilization of cardiovascular medications.

Not only does Applicants' invention represent an attempt to provide a prophylactic therapy in a single dosage unit to address the above-mentioned problems, but Applicants' invention also attempts to improve upon the under-utilization of these specific medications, namely beta-blockers and an antihyperlipidemic agents. Under-utilization is clearly a concern of the medical profession. Particularly, health plan organizations are continually looking for effective ways to improve health outcomes and lower costs. Dr. Dean's Declaration along with supporting exhibits was previously submitted in support of the above conclusions. Even though opinion testimony by a party with a direct interest in the litigation is less persuasive than that of a disinterested party, but it may still be relied upon. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). Dr. Dean's extensive experience in the healthcare industry is still relied upon to support the above conclusions.

Furthermore, various exhibits (McCormick et al. and Hedis 2000) were previously submitted as evidence that the use of beta-blockers and lipid lowering medications are under utilized. These exhibits are objective evidence composed of real world facts.

This evidence is entitled to great weight. Dr. Dean's Declaration clearly reinforces the fact that these problems have existed for some time and continue to exist. Under-utilization is clearly a concern of the medical profession.

Applicants further submit new evidence that the problems still exist in the medical field. Exhibit 3, submitted herewith, is a study/investigation by Vittinghoff et al. entitled "Risk Factors and Secondary Prevention in Women with Heart Disease: The Heart and Estrogen/progestin Replacement Study", Annals of Internal Medicine, Vol. 138, No. 2, January 21, 2003, pages 81-89. This recent study further concludes that women with coronary disease are at high risk for myocardial infarction or death from coronary heart disease even in the absence of other risk factors, and their risk increases up to six-fold when many risk factors are present. Established drugs for secondary prevention, including aspirin, beta-blockers, and lipid lowering agents are underused in these women, especially those at higher risk.

date of publication after the filing date

Exhibit 4, submitted herewith, is an editorial entitled "Secondary Prevention of Coronary Heart Disease in Women: A Call to Action", Annals of Internal Medicine, Vol. 138, No. 2, January 21, 2003, pages 150-151. This article discusses the findings in the Vittinghoff et al. analysis (an alarming underutilization of proven therapies) and the consistent results of studies showing that the use of postmenopausal hormones for prevention or treatment of coronary heart disease in women actually increased coronary heart disease events in the first year of treatment and increased stroke and venous thromboembolic events. The article further discloses that despite clear

indications for these therapies, women with more risk factors, and hence more potential benefit, were less likely than those with no risk factors to receive aspirin or other antiplatelet drugs or lipid-lowering therapy. Consequently, the article issues a *call to action to implement tools* to prevent coronary heart disease events in women.

These articles recognize the need and the difficulties encountered to better utilize beta blockers and lipid-lowering medications. The appearance of these articles years after it was known by those skilled in the art that beta blockers and lipid-lowering medications are still under-utilized reinforces the difficulties encountered by those skilled in the field. These are classical indicia of nonobviousness.

Dr. Gurwitz's Declaration clearly indicates that one of ordinary skill in the art considers Applicants' invention to be novel and nonobvious in providing a potential solution to compliance and under-utilization of these medications. Dr. Gurwitz's Declaration also clearly indicates that the healthcare industry's focus is now and has always been to educate healthcare providers and patients, not to providing novel means for achieving better patient compliance and utilization results. Further, Dr. Gurwitz's Declaration reinforces Dr. Dean's opinion as to the state of the art regarding compliance and under utilization. An expert's affidavit of firsthand practical knowledge of unsolved needs in the art is evidence of the state of the art. In re Piesecki, 745 F. 2d 1468, 223 USPQ 785 (Fed. Cir. 1984).

The present application specifically addresses the failure of patients to receive these treatments and seeks to improve it, as stated on Page 5, lines 21-24 of

Applicants' disclosure:

> The clear need for cardiovascular preventive treatment and the failure of patients to avail themselves of such treatment underscores the present need for the formulations of this invention.

Nowhere in any of the cited prior art is it suggested to combine these multiple medicaments into a single dosage unit to simplify treatment, increase convenience, reduce cost, increase utilization of various medications, and enhance patient compliance. The Office admits that none of the prior art provides the motivation to combine beta-blockers and cholesterol-lowering agents into a single dosage unit.

Applicants further submit that the cited references merely recite cardiovascular medications and contain no teaching or suggestion relating to the failure of patients to receive particular treatments. The references cited neither acknowledge this problem nor contain any suggestion for improving upon it. The haphazard combining of medications, even those known to have cardiovascular usage, would not improve upon this problem.

This problem has also been overlooked by the pharmaceutical industry despite considerable motivation, i.e. increased sales, to increase usage of medication.

Applicants submit that without some teaching or suggestion in the prior art that addresses solutions to the problem of the failure of patients to receive specific cardiovascular treatments, the present invention would be obvious only in hindsight.

It is clear that when Applicants' invention is viewed as a whole the prior art contains no suggestion to combine Applicants' cardiovascular treatment medications

into a single dosage unit. Where Applicants' components are similar to those components shown and disclosed in the prior art, the law requires that the prior art also contain some teaching, suggestion or incentive for arriving at Applicants' claimed structure. The Office has failed to provide this showing. In fact, the Office admits that the prior art does not provide this teaching, suggestion or motivation. The Office states that one of ordinary skill in the art would have been motivated to combine the medications into a single dosage unit because they are known to be useful for the same purpose. The Office relies on its conclusion based on In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

The Office's reliance is misplaced and Kerkhoven is inapposite. Kerkhoven is a process claim case and cites to In re Crockett, 279 F.2d 274 (CCPA 1960), which contains the reference that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful **for the same purpose**, in order to form a third composition which is to be used for the **very same purpose**. The ruling is based on the use of two compositions, each of which promotes the formation of a nodular structure in cast iron.

The ruling in Kerkhoven is inappropriate in the present application because the two compositions of the present application are not used for the **very same purpose**. The purpose of beta-blockers is to block nerve impulses to special sites (beta receptors) and to reduce the rate of heartbeats and the force of heart contractions. In other words, beta blockers tend to reduce the heart's workload and stress. The

different mechanism of action but for the same purpose

purpose of lipid-lowering agents is to reduce or prevent the deposit of arterial plaque along the walls of the arteries by suppressing total cholesterol in the blood. Lipid-lowering agents, unlike beta blockers, do not reduce heartbeat rate or contraction force. Conversely, beta-blockers cannot be used for reducing total blood cholesterol. Each medication serves a **different** purpose in a treatment regimen for cardiovascular disease. Where the purpose of beta-blockers and cholesterol-lowering agents are **not the same**, Kerkhoven is inapposite.

In accordance with the more recent rulings of the Federal Circuit, the Office must point to some teaching, suggestion or incentive in the cited prior art for arriving at the claimed structure. The Office has failed to do this. In fact, the Office admits that the prior art does not teach the use of beta-blockers and cholesterol-lowering agents in a single dosage unit.

The Office has fallen into the hindsight trap. The idea of a beta-adrenergic blocker and a lipid-lowering agent that is a statin being combined as a single oral formulation as opposed to multiple agents being delivered by multiple oral formulations is a technologically simple concept. With this simple concept in mind, the Office found prior art statements that in the abstract appeared to suggest the claimed limitation. But the Office points to no specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of Dean et al.'s invention to make the combination in the manner claimed. On the other hand, Applicants' have submitted the Declarations of Dr. Gurwitz and Dr. Dean in support of

the state of the art.

Further, the solutions to problems with compliance and under-utilization of helpful medications for cardiovascular treatments are elusive, and have troubled the healthcare industry for a long time. The industry continues to struggle to find answers to these perplexing questions as further evidenced by Exhibits 3 and 4 submitted herewith. The healthcare industry's focus is now and has always been to educate physicians and patients, not to providing novel means for achieving better patient compliance and utilization results. Dr. Gurwitz's declaration as well as Dr. Dean's declaration are evidence that the healthcare industry's approach is to educate physicians and patients.

Similarly, this problem has been overlooked by the pharmaceutical industry despite considerable motivation, i.e. increased sales, to increase usage of medication.

Applicants submit that without some teaching or suggestion in the prior art that addresses solutions to the problem of the failure of patients to receive specific cardiovascular treatments and to improve compliance, the present invention would be obvious only in hindsight.

Conclusion

It is clear that when Applicants' invention is viewed as a whole the prior art contains no suggestion to combine Applicants' cardiovascular treatment medications into a single dosage unit. Where Applicants' components are similar to those components shown and disclosed in the prior art, the law requires that the prior art also

contain some teaching, suggestion or incentive for arriving at Applicants' claimed structure. The Office has failed to provide this showing. On the other hand, Applicants have provided evidence of noncompliance problems, the under-utilization of medications and the Declarations of Dr. Gurwitz and Dr. Dean (previously submitted) as to the healthcare industries' struggles to find answers to these perplexing questions.

In light of the above arguments, Applicants respectfully submit that Claims 1-10 and 17-18 of the present application contain allowable subject matter and that the 35 USC §103(a) rejections have been successfully traversed.

Applicants believe that all of the pending claims should now be in condition for allowance. Early and favorable action is respectfully requested.

The Examiner is invited to telephone the undersigned, Applicant's attorney of record, to facilitate advancement of the present application.

Respectfully submitted,

Dated: 6-24-03

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450, on:

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